requires one field study to be conducted at multiple locations, FDA will provide justification for requiring multiple locations verbally during the presubmission conference and in writing as part of the memorandum of conference.

(g) *Modification of presubmission conference agreements.* An agreement made under a presubmission conference requested under section 512(b)(3) of the act and documented in a memorandum of conference is binding on the potential applicant and FDA and may only be modified if:

(1) FDA and the potential applicant mutually agree to modify, in part or in whole, the agreement and such modification is documented and provided to the potential applicant as described in paragraph (f)(1) of this section; or

(2) FDA by written order determines that a substantiated scientific requirement essential to the determination of safety or effectiveness of the new animal drug appeared after the conference.

(h) *When the terms of a presubmission conference agreement are not valid*—(1) A presubmission conference agreement will no longer be valid if:

(i) The potential applicant makes to FDA, before, during, or after the presubmission conference, any untrue statement of material fact; or

(ii) The potential applicant fails to follow any material term of the agreement; and

(2) A presubmission conference may no longer be valid if the potential applicant submits false or misleading data relating to a new animal drug to FDA.

(i) *Dispute resolution.* FDA is committed to resolving differences between a potential applicant and FDA reviewing divisions with respect to requirements for the investigation of new animal drugs and for NADAs, supplemental NADAs, and ANADAs as quickly and amicably as possible through a cooperative exchange of information and views. When administrative or procedural disputes arise, a potential applicant should first attempt to resolve the matter within the appropriate review division beginning with the individual(s) most directly assigned to the review of the application or investigational exemption. If the dispute cannot be resolved after such attempts, the dispute shall be evaluated and administered in accordance with applicable regulations (21 CFR 10.75). Dispute resolution procedures may be further explained by guidance available from the Center for Veterinary Medicine.

[69 FR 51170, Aug. 18, 2004]

§ 514.6 Amended applications.

The applicant may submit an amendment to an application that is pending, including changes that may alter the conditions of use, the labeling, safety, effectiveness, identity, strength, quality, or purity of the drug or the adequacy of the manufacturing methods, facilities, and controls to preserve them, in which case the unamended application may be considered as withdrawn and the amended application may be considered resubmitted on the date on which the amendment is received by the Food and Drug Administration. The applicant will be notified of such date.

§ 514.7 Withdrawal of applications without prejudice.

The sponsor may withdraw his pending application from consideration as a new animal drug application upon written notification to the Food and Drug Administration. Such withdrawal may be made without prejudice to a future filing. Upon resubmission, the time limitation will begin to run from the date the resubmission is received by the Food and Drug Administration. The original application will be retained by the Food and Drug Administration although it is considered withdrawn. The applicant shall be furnished a copy at cost on request.

§ 514.8 Supplements and other changes to an approved application.

(a) *Definitions.* (1) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to those terms when used in this part.

(2) The following definitions of terms apply to this part:

(i) *Assess the effects of the change* means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency

of a drug as these factors may relate to the safety or effectiveness of the drug.

(ii) *Drug substance* means an active ingredient as defined under § 210.3(b)(7) of this chapter.

(iii) *Minor changes and stability report (MCSR)* means an annual report that is submitted to the application once each year within 60 days before or after the anniversary date of the application's original approval or on a mutually agreed upon date. The report must include minor manufacturing and control changes made according to § 514.8(b)(4) or state that no changes were made; and stability data generated on commercial or production batches according to an approved stability protocol or commitment.

(iv) *Specification* means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drugs including, for example, drug substances, Type A medicated articles, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug. For the purpose of this definition, the term ''acceptance criteria'' means numerical limits, ranges, or other criteria for the tests described.

(b) *Manufacturing changes to an approved application*—(1) *General provisions.* (i) The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about it in a supplement under paragraph (b)(2) or (b)(3) of this section or by inclusion of the information in the annual report to the application under paragraph (b)(4) of this section.

(ii) The holder of an approved application under section 512 of the act must assess the effects of the change before distributing a drug made with a manufacturing change.

(iii) Notwithstanding the requirements of paragraphs (b)(2) and (b)(3) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the drug, or by notification in the next annual report described in paragraph (b)(4) of this section).

(iv) In each supplement and amendment to a supplement providing for a change under paragraph (b)(2) or (b)(3) of this section, the applicant must include a statement certifying that a field copy has been provided to the appropriate FDA district office. No field copy is required for a supplement providing for a change made to a drug manufactured outside of the United States.

(v) A supplement or annual report described in paragraph (b)(4) of this section must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(2) *Changes requiring submission and approval of a supplement prior to distribution of the drug made using the change (major changes).* (i) A supplement must be submitted for any change in the drug, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug.

(ii) These changes include, but are not limited to:

(A) Except those described in paragraphs (b)(3) and (b)(4) of this section, changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications provided in the approved application;

(B) Changes requiring completion of appropriate clinical studies to demonstrate the equivalence of the drug to the drug as manufactured without the change;

(C) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(D) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(E) Changes in a drug product container closure system that controls the drug delivered to the animal or changes in the type or composition of a packaging component that may affect the impurity profile of the drug product;

(F) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(*1*) Changes in the virus or adventitious agent removal or inactivation method(s),

(*2*) Changes in the source material or cell line, and

(*3*) Establishment of a new master cell bank or seed;

(G) Changes to a drug under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(iii) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug made using a change under paragraph (b)(2) of this section. The supplement must be labeled ''Prior Approval Supplement.'' Except for submissions under paragraph (b)(2)(v) of this section, the following information must be contained in the supplement:

(A) A completed Form FDA 356V;

(B) A detailed description of the proposed change;

(C) The drug(s) involved;

(D) The manufacturing site(s) or area(s) affected;

(E) A description of the methods used and studies performed to assess the effects of the change;

(F) The data derived from such studies;

(G) Appropriate documentation (for example, updated master batch records, specification sheets) including previously approved documentation (with the changes highlighted) or references to previously approved documentation;

(H) For a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and standard operating procedures must be provided in addition to the requirements in paragraphs (b)(2)(iii)(E) and (b)(2)(iii)(F) of this section;

(I) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(2)(iii)(E) and (b)(2)(iii)(F) of this section; and

(J) Any other information as directed by FDA.

(iv) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover must be plainly marked: ''Prior Approval Supplement-Expedited Review Requested.''

(v) *Comparability Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of the drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect. A comparability protocol supplement must be labeled ''Prior Approval Supplement—Comparability Protocol.''

(3) *Changes requiring submission of a supplement at least 30 days prior to distribution of the drug made using the change (moderate changes).* (i) A supplement must be submitted for any change in the drug, production process,

quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug.

(ii) These changes include, but are not limited to:

(A) A change in the container closure system that does not affect the quality of the drug except as otherwise described in paragraphs (b)(2) and (b)(4) of this section;

(B) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(*1*) An increase or decrease in production scale during finishing steps that involves different equipment, and

(*2*) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(C) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(iii) A supplement submitted under paragraph (b)(3)(i) or (b)(3)(vi) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is made. The supplement submitted under paragraph (b)(3)(i) must be labeled ''Supplement-Changes Being Effected in 30 Days.''

(iv) Pending approval of the supplement by FDA and except as provided in paragraph (b)(3)(vi) of this section, distribution of the drug made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(2)(iii)(A) through (b)(2)(iii)(J) of this section must be contained in the supplement.

(v) The applicant must not distribute the drug made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(A) The change requires approval prior to distribution of the drug in accordance with paragraph (b)(2) of this section; or

(B) Any of the information required under paragraph (b)(3)(iv) of this section is missing. In this case, the applicant must not distribute the drug made using the change until the supplement has been amended to provide the missing information.

(vi) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug involved upon receipt by the agency of a supplement for the change. The information listed in paragraphs (b)(2)(iii)(A) through (b)(2)(iii)(J) of this section must be contained in the supplement. The supplement must be labeled ''Supplement-Changes Being Effected.'' These changes include, but are not limited to:

(A) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess; and

(B) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another.

(vii) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug(s) made with the manufacturing change.

(4) *Changes and updated stability data to be described and submitted in an annual report (minor changes).* (i) Changes in the drug, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug must be documented by the applicant in an annual report to the application as described under paragraph (a)(2)(iii) of this section. The report must be labeled ''Minor Changes and Stability Report.''

(ii) These changes include but are not limited to:

(A) Any change made to comply with a change to an official compendium,

except a change in paragraph (b)(3)(ii)(C) of this section, that is consistent with FDA statutory and regulatory requirements;

(B) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(C) Replacement of equipment with that of the same design and operating principles except for those equipment changes described in paragraph (b)(3)(ii)(B)(2) of this section;

(D) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug product, without a change from one container closure system to another;

(E) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(F) An extension of an expiration dating period based upon full shelf-life data on production batches obtained from a protocol approved in the application;

(G) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the drug being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure; and

(H) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint.

(iii) For changes under this category, the applicant is required to submit in the annual report:

(A) A completed Form FDA 356V;

(B) A statement by the holder of the approved application that the effects of the change have been assessed;

(C) A detailed description of the change(s);

(D) The manufacturing site(s) or area(s) involved;

(E) The date each change was implemented;

(F) Data from studies and tests performed to assess the effects of the change;

(G) For a natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, relevant validation protocols and/or standard operating procedures;

(H) Appropriate documentation (for example, updated master batch records, specification sheets, etc.) including previously approved documentation (with the changes highlighted) or references to previously approved documentation;

(I) Updated stability data generated on commercial or production batches according to an approved stability protocol or commitment; and

(J) Any other information as directed by FDA.

(c) *Labeling and other changes to an approved application*—(1) *General provisions.* The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully.

(2) *Labeling changes requiring the submission and approval of a supplement prior to distribution of the drug made using the change (major changes).* (i) Addition of intended uses and changes to package labeling require a supplement. These changes include, but are not limited to:

(A) Revision in labeling, such as updating information pertaining to effects, dosages, adverse reactions, contraindications, which includes information headed ''adverse reactions,'' ''warnings,'' ''precautions,'' and ''contraindications,'' except ones described in (c)(3) of this section;

(B) Addition of an intended use;

(C) If it is a prescription drug, any mailing or promotional piece used after the drug is placed on the market is labeling requiring a supplemental application, unless:

(*1*) The parts of the labeling furnishing directions, warnings, and information for use of the drug are the same

in language and emphasis as labeling approved or permitted; and

(*2*) Any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling.

(*3*) Prescription drug labeling not requiring an approved supplemental application is submitted in accordance with § 514.80(b)(5)(ii).

(D) Any other changes in labeling, except ones described in paragraph (c)(3) of this section.

(ii) The applicant must obtain approval of the supplement from FDA prior to distribution of the drug. The supplement must contain the following:

(A) A completed Form FDA 356V;

(B) A detailed description of the proposed change;

(C) The drug(s) involved;

(D) The data derived from studies in support of the change; and

(E) Any other information as directed by FDA.

(3) *Labeling changes to be placed into effect prior to receipt of a written notice of approval of a supplemental application.* (i) Labeling changes of the following kinds that increase the assurance of drug safety proposed in supplemental applications must be placed into effect immediately:

(A) The addition to package labeling, promotional labeling, or prescription drug advertising of additional warning, contraindication, adverse reaction, and precaution information;

(B) The deletion from package labeling, promotional labeling, or drug advertising of false, misleading, or unsupported intended uses or claims for effectiveness; and

(C) Any other changes as directed by FDA.

(ii) Labeling changes (for example, design and style) that do not decrease safety of drug use proposed in supplemental applications may be placed into effect prior to written notice of approval from FDA of a supplemental application.

(iii) A supplement submitted under paragraph (c)(3) of this section must include the following information:

(A) A full explanation of the basis for the changes, the date on which such changes are being effected, and plainly marked on the mailing cover and on the supplement, ''Supplement—Labeling Changes Being Effected'';

(B) Two sets of printed copies of any revised labeling to be placed in use, identified with the new animal drug application number; and

(C) A statement by the applicant that all promotional labeling and all drug advertising will promptly be revised consistent with the changes made in the labeling on or within the new animal drug package no later than upon approval of the supplemental application.

(iv) If the supplemental application is not approved and the drug is being distributed with the proposed labeling, FDA may initiate an enforcement action because the drug is misbranded under section 502 of the act and/or adulterated under section 501 of the act. In addition, under section 512(e) of the act, FDA may, after due notice and opportunity for a hearing, issue an order withdrawing approval of the application.

(4) *Changes providing for additional distributors to be reported under Records and reports concerning experience with approved new animal drugs (§ 514.80).* Supplemental applications as described under paragraph (c)(2) of this section will not be required for an additional distributor to distribute a drug that is the subject of an approved new animal drug application or abbreviated new animal drug application if the conditions described under § 514.80(b)(5)(iii) are met.

(d) *Patent information.* The applicant must comply with the patent information requirements under section 512(c)(3) of the act.

(e) *Claimed exclusivity.* If an applicant claims exclusivity under section 512(c)(2)(F) of the act upon approval of a supplemental application for a change in its previously approved drug, the applicant must include such a statement.

(f) *Good laboratory practice for nonclinical laboratory studies.* A supplemental application that contains nonclinical laboratory studies must include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this

chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

[71 FR 74782, Dec. 13, 2006]

§ 514.11 Confidentiality of data and information in a new animal drug application file.

(a) For purposes of this section the *NADA file* includes all data and information submitted with or incorporated by reference in the NADA, INAD's incorporated into the NADA, supplemental NADA's, reports under §§ 514.80 and 510.301 of this chapter, master files, and other related submissions. The availability for public disclosure of any record in the NADA file shall be handled in accordance with the provisions of this section.

(b) The existence of an NADA file will not be disclosed by the Food and Drug Administration before an approval has been published in the FEDERAL REGISTER, unless it has previously been publicly disclosed or acknowledged.

(c) If the existence of an NADA file has not been publicly disclosed or acknowledged, no data or information in the NADA file is available for public disclosure.

(d) If the existence of an NADA file has been publicly disclosed or acknowledged before an approval has been published in the FEDERAL REGISTER, no data or information contained in the file is available for public disclosure before such approval is published, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(e) After an approval has been published in the FEDERAL REGISTER, the following data and information in the NADA file are immediately available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information previously disclosed to the public, as defined in § 20.81 of this chapter.

(2) A summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the NADA file. Such summaries do not constitute the full reports of investigations under section 512(b)(1) of the act (21 U.S.C. 360b(b)(1)) on which the safety or effectiveness of the drug may be approved. Such summaries shall consist of the following:

(i) For an NADA approved prior to July 1, 1975, internal agency records that describe such data and information, e.g., a summary of basis for approval or internal reviews of the data and information, after deletion of:

(*a*) Names and any information that would identify the investigators.

(*b*) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.

(ii) For an NADA approved on or after July 1, 1975, a summary of such data and information prepared in one of the following two alternative ways shall be publicly released when the approval is published in the FEDERAL REGISTER.

(*a*) The Center for Veterinary Medicine may at an appropriate time prior to approval of the NADA require the applicant to prepare a summary of such data and information, which will be reviewed and, where appropriate, revised by the Center.

(*b*) The Center for Veterinary Medicine may prepare its own summary of such data and information.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61 of this chapter.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician, hospital, or other institution.

(5) A list of all active ingredients and any inactive ingredients previously